Therapeutic and Persistent Efficacy of a Single Application of Doramectin Applied Either as a Pour-on or Injection to Cattle Infested with *Boophilus microplus* (Acari: Ixodidae)

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ABSTRACT The efficacy of a single treatment with a pour-on application or a subcutaneous injection of the macrocyclic lactone endectocide, doramectin, was evaluated in separate trials on Hereford heifers infested with *Boophilus microplus* (Canestrini). Significantly fewer ticks per calf were recovered from both groups of treated animals than from the complimentary untreated calves. The mean weights of engorged females and egg masses from both pour-on–treated and injectable-treated calves were also significantly smaller than the complimentary variables for the two groups of untreated calves. Among the treated groups, the mean weight of females from calves treated with the subcutaneous injection was 55% less than females from cattle that received the pour-on treatment and the weights of egg masses were 71% lighter than those from the pour-on–treated group. The estimates of percentage control for the two treatments were 88.6 for the pour-on formulation and a notably higher 99.8 for the injectable formulation. To obtain estimates of the effect of the treatments on the parasitic stages of the tick, cattle were infested with *B. microplus* larvae at three weekly intervals beginning 18 d pretreatment to ensure that, on the day of treatment, ticks in all three parasitic stages (adult, nymph, larva) would be on the cattle. The effect of the treatments on each parasitic stage was estimated by partitioning detached females into three groups by noting in which of the three 7-d intervals after detachment of engorged females began that detachment occurred. There was no difference for either the pour-on or injectable in the effect of the specific treatment on each parasitic stage. The persistent efficacy of the pour-on treatment against larvae placed on the hosts 1 wk after treatment was zero. The persistent efficacy of the injectable treatment ranged from 100 to 82.1% (mean, 93.7%) against the larvae placed on calves the first 3 wk after treatment and was still 44% against the fourth weekly posttreatment infestation. The injectable doramectin is a potential alternative to the coumaphos product now used as a precautionary treatment at USDA, Veterinary Services, Livestock Import Stations, for cattle exported from Mexico.

KEY WORDS *Boophilus microplus*, control, macrocyclic lactone, southern cattle tick, doramectin

THE WIDESPREAD OCCURRENCE IN Mexico of populations of *Boophilus microplus* (Canestrini) that are resistant to coumaphos and other organophosphate (OP) acaricides is reason for questioning the prudence of continued reliance on coumaphos as a dip for cattle at the Livestock Import Stations of the U.S. Department of Agriculture's Animal and Plant Health Inspection Service, Veterinary Services (USDA, APHIS, VS). If inspectors at one of these stations located in Mexico near the Texas-Mexico border fail to detect OP-resistant ticks on cattle presented for export to the United States and approve them for entry, there is substantial risk that some of the resistant ticks could survive immersion of their hosts in the precautionary dip of coumaphos before export to become the progenitors of a population of resistant ticks in south Texas (Davey and George 1999). Formamidines (amitraz), pyrethroids, and macrocyclic lactone endectocides are the only alternatives to coumaphos for use at the import stations, but resistance to amitraz and pyrethroids eliminates these two chemical groups of acaricides from consideration. Laboratory and field trials with the macrocyclic lactone products ivermectin (Campbell et al. 1983, Cramer et al. 1988), eprinomectin (Davey and George 2002), moxidectin (Remington et al. 1997, Guglielmone et al. 2000), and doramectin (Gonzales et al. 1993, Caproni et al. 1998) proved the efficacy of these acaricides for the control of *B. microplus* on pastured and stanchioned cattle. Usually, treatments with one of the macrocyclic lactones for tick control would be administered by applying a pour-on, or possibly, by a subcutaneous injection.

This article reports the results of research only. Mention of a proprietary product does not constitute an endorsement or a recommendation by the USDA for its use.

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When cattle are brought to the Mexico-Texas border for export, it is important for them to be inspected and processed with minimal handling and in a timely fashion to minimize stress, weight loss, and extra costs for feed and handling. When a lot of cattle from Mexico is brought to one of the VS Livestock Import Stations, it must be accompanied by certification from a Mexican veterinarian that the animals have been dipped within the last 10–14 d. Each animal is examined for ticks. If even a single tick is discovered, the entire lot of cattle is rejected. If no ticks are found and all other animal health criteria have been satisfied, the cattle are dipped in a vat charged with 0.3% (AI) coumaphos and released for export to the United States. Coumaphos kills ticks rapidly, and even replete females from a coumaphos-susceptible strain that are attached to an animal dipped in the high concentration of coumaphos at an import facility will not survive the treatment, and it is safe to bring the cattle into the United States immediately (Davey and Ahrens 1982). Ideally, the dynamics of the lethal effects of an acaricide considered as an alternative to coumaphos would parallel those of coumaphos. If the time from treatment to the onset of lethal effects is different from coumaphos or if the effect of a treatment on the three parasitic stages of a *Boophilus* tick varies, these factors must be taken into consideration in the design, and implementation of changes in the acaricide and regulations for treating the cattle destined for export to the United States.

The purpose of this study was to evaluate the therapeutic and persistent efficacy of a single treatment of *B. microplus*–infested cattle with a pour-on formulation or a subcutaneous injection of doramectin with an experimental design that enables a determination of not only the overall effect on the ticks but also an estimate of therapeutic efficacy against each of the three parasitic stages. This approach will facilitate critical assessment of the usefulness of the treatments to protect against introductions of ticks on imported cattle and to establish the basis of a strategy for treating and releasing cattle for export. Experimental results will also indicate the potential usefulness of the two doramectin formulations for treating cattle to eradicate tick outbreaks in the quarantine zone or adjacent tick-free area and other aspects of the Cattle Fever Tick Eradication Program (CFTEP) of APHIS, VS.

Materials and Methods

The investigation was done at the U.S. Department of Agriculture, Agricultural Research Service, Cattle Fever Tick Research Laboratory, Mission, TX. The research consisted of two separate trials each designed to provide an estimate of the therapeutic and persistent efficacy of two different formulations: an injectable and a pour-on formulation of doramectin. They were applied to cattle infested with adult, nymphal, and larval *B. microplus* at the time of treatment.

The trials were conducted separately. Naive cattle were used in each of the trials to prevent or reduce bias caused by using cattle previously challenged with ticks. All cattle in each trial were maintained individually in stanchions inside an open-sided barn in 3.3 by 3.3 m stalls separated by 1.7-m-high cinder block walls. Each trial was conducted under ambient conditions, except that no direct sunlight or rainfall reached the cattle because of the barn roof.

The two formulations of doramectin, Dectomax Pour-on (Doramectin 0.5% Pour-on) and Dectomax Injectable (Doramectin 1% Injectable Solution), are registered products of Pfizer Animal Health, Newark, NJ. In the United States, the two products are registered for use against a variety of internal and external parasites, excluding ticks. The pour-on formulation contained 5 mg/ml (0.5%) (AI), and the treatment was applied to infested cattle at the rate of 1 ml/10 kg of animal body weight, which was the labeled registered treatment dose. The treatment method for the pour-on application consisted of measuring the appropriate volume of endectocide into a graduated cylinder and evenly applying the material along the midline of the back of each calf from the withers to the tail head. The doramectin injectable was administered subcutaneously at a dose rate of 200 μg/kg (1 ml/50 kg).

Evaluation of Therapeutic Efficacy. Other than the differences in the two formulations and the methods used to treat animals, all procedures followed in conducting trials with the pour-on and the injectable were the same. Eight Hereford heifer calves weighing ≈200 kg each were used in each trial. The calves in each trial were randomly divided into two equal groups containing four calves per group. In each trial, the estimate of therapeutic efficacy of each formulation was based on three separate larval infestations made on each calf before the initiation of the treatment. All infestations on cattle in both trials were made by applying 17 by 60 mm (2-dram) shell vials containing ≈5,000 larvae that were 2–4 wk old to the front shoulder area of each calf using branding cement. After the vial was secure, the cotton plug that held the larvae inside the vial was removed to allow larvae to move freely over the body of the calf. In both trials, each calf was infested 18 d before the initiation of treatment, and two additional infestations of ≈5,000 larvae each were made at 11 and 4 d before the initial treatment. This infestation pattern allowed for the evaluation of the efficacy of the endectocides against adult, nymphal, and larval ticks at the time treatment was initiated.

The eight calves used in each of the trials were weighed individually on the day the treatment was applied, so that the appropriate volume of test material for each animal could be calculated, and each calf was treated with the appropriate doramectin formulation in the manner previously described. In each of the two trials, the first group of calves was treated with one of the formulations. The second group of cattle in each trial remained as an untreated control group.

Once the treatment was applied to cattle in each of the trials, data were collected on each calf in each treatment group for a period of 23 d (26 d after the last

pretreatment larval infestation). This 23-d posttreatment evaluation period was based on the report that, ≈20 d after larval infestation, the first detachment of *B. microplus* occurs and that >95% of all engorged females infested at a given time would detach from the host within 26 d after infestation (Hitchcock 1955). On each day of the posttreatment evaluation period (both trials), all females that detached from each calf were collected and counted. A random sample of 10 engorged females was saved each day from each calf, whenever possible, to obtain weight, fecundity, and fertility data. Engorged females from each daily collection sample on each calf were weighed collectively, placed in a 9-cm-diameter petri dish, and incubated at 27 ± 2°C, 92% RH, under a (L:D) 12:12 h photoperiod. Females were allowed to oviposit for 20 d, after which the spent females were discarded, and the eggs were weighed, placed in a coded 25 by 93 mm (8-dram) shell vial, and returned to the incubator. After 4 wk, the percentage of egg hatch from each sample group was visually estimated using a stereo-microscope with an ocular grid, by comparing the proportion of larvae in relation to the proportion of unhatched eggs.

After all data (tick counts, egg mass weights, and percentage of egg hatch) were collected over the 23-d evaluation period, the index of fecundity (IF) was calculated for each calf for each day using the following formula (Davey et al. 2001):

$$\text{IF} = \text{Total no. of } ♀♀ \text{ collected} \times \frac{\text{Weight of eggs}}{\text{No. of } ♀♀ \text{ sampled}} \times \text{Egg hatch (\%)}$$

Thus, the IF value is an estimate of the reproductive potential of a given number of females that lay a given quantity of eggs with a given hatching rate. The biological data (female weight and egg mass weight) were also used to provide an indication of whether the endectocide treatments had a measurable sublethal effect on the size and fecundity of the females that survived to repletion after treatment.

The 23 daily IF values for each calf were summed to obtain a total IF value for each animal. The total IF values for each calf in the control group were averaged to obtain a single mean IF value for the control group. This average IF value for the control group was compared with the total IF value for each of the endectocide-treated groups to obtain the percentage control of each endectocide using the following formula (Abbott 1925):

$$\%\ \text{Control} = \frac{\text{Mean total IF; control group} - \text{Total IF of each calf; treated group}}{\text{Mean total IF; control group}} \times 100$$

Infesting cattle with larvae at 7-d intervals provided the means for classifying and analyzing the effect of each of the doramectin treatments on each parasitic stage (adult, nymph, larva). Engorged females that detached days 2–8 after treatment were considered to have been in the adult stage the day treatment was administered. All females collected 9–15 d after treatment were considered to have been nymphs on the day of treatment. Similarly, all females collected 16–23 d after treatment were considered to have been larvae on the day of treatment. After daily IF values for each animal were calculated for both treated and untreated animals, the sums were partitioned to obtain total IFs/animal for each of the three 7-d intervals that corresponded to the estimated life stage of each of the three groups of females at the time of treatment. A mean total IF was calculated for each of the three sets of data from each treatment. A two-way analysis of variance (ANOVA) and Student-Neuman-Keuls test was used to compare tick numbers, engorged female weights, egg mass weights, and treated and untreated IF by treatment and life stage at the time of treatment. The CoStat software (CoHort Software 2001) used for statistical analysis of all data obtained in the study uses a general linear model (GLM) technique to solve ANOVAs.

Evaluation of Persistent Efficacy. Estimates of the persistent effectiveness of the pour-on and injectable formulations of doramectin were based on a series of tick infestations of treated and untreated cattle made at regular intervals beginning 1 wk after the treatments were administered. Infestation procedures were identical to those described above. Larvae (≈5,000) were placed on each calf beginning 1 wk after treatment and continuing at weekly intervals through the fourth week after treatment. Engorged females that detached 27–33 d after treatment were classified as originating from the 1-wk posttreatment infestation; females that detached 34–40 d after treatment were classified as originating from the second weekly posttreatment infestation; females that detached 41–47 d after treatment were classified as originating from the third posttreatment infestation; and females that detached 48–54 d after treatment were classified as originating from the fourth weekly posttreatment infestation.

Beginning 27 d after treatment and continuing consecutively through day 54 after treatment, engorged females that detached from each animal were collected and counted. From each daily collection from each animal, a random sample of 10 engorged females (whenever possible) was saved to obtain data on fecundity and fertility, as described above. After all data (tick counts, egg mass weights, and egg hatch) had been collected, the IF of ticks recovered from each animal on each day between day 27 and day 54 after treatment was calculated as described above. Once the IF of ticks from each animal on each day was calculated, the values for the four animals within each of the treatment and control groups were averaged to obtain the mean daily IF. After the mean daily IF values of each treatment and control group were calculated, they were summed over 7-d intervals, each of which corresponded to one of the four posttreatment classifications. The percent control of the IF resulting from the injectable or pour-on treatment at each of the four weekly posttreatment intervals was determined

Table 1. Mean ± SD tick number per calf and percentage control of the IF of *B. microplus* on untreated cattle, cattle treated with a single pour-on application of doramectin at 0.5% AI, or cattle treated with a single subcutaneous injection of doramectin at 200 μg AI/kg body weight

Treatment	*n*	Number of ticks per calf	Control of the IF (%)
Untreated	4	2489 ± 782 a	—
Pour-on treatment	4	940 ± 335 b	88.6 ± 4.5
Untreated	4	3013 ± 1622 a	—
Injectable treatment	4	470 ± 392 b	99.8 ± 0.46

Means within the same column followed by the same letter are not significantly different ($P = 0.05$).

by comparing the total IF of the untreated group with the total IF of the corresponding treated group having the same weekly posttreatment classification as described above. The same methods of statistical analysis applied to data for the therapeutic treatment were used in the analysis of data related to residual efficacy.

In conducting the research described in this report, the investigators adhered to protocol approved by the USDA–ARS Animal Welfare Committee. The protocol is on file at the Knipling-Bushland U.S. Livestock Insects Laboratory, Tick Research Unit, USDA–ARS, Kerrville, TX.

Results

Doramectin Pour-on Treatment. The mean number of engorged females per calf recovered from treated animals was significantly lower ($F = 12.6$; df = 1, 7; $P < 0.02$) than from the untreated calves (Table 1). The degree of therapeutic control that resulted from the pour-on treatment was 88.6%. The mean weight of an engorged female from treated calves was 73% less than engorged females from untreated calves. The difference in mean female weight was statistically significant ($F = 288.7$; df = 7, 174; $P < 0.0001$; Table 2). Mean weights of egg masses from females recovered from treated calves were significantly smaller ($F = 129.2$; df = 7, 174; $P < 0.0001$) than those oviposited by females from untreated calves.

There was a statistically significant effect of the pour-on treatment on the IF of ticks from treated and untreated females ($F = 9.97$; df = 5, 23; $P < 0.0001$).

Table 2. Mean ± SD female weight and egg mass weight of *B. microplus* females recovered from untreated cattle, cattle treated with a single pour-on application of doramectin at 0.5% AI, or cattle treated with a single subcutaneous injection of doramectin at 200 μg AI/kg body weight

Treatment	*n*	Female weight (mg)	Egg mass weight (mg)
Untreated	88	355 ± 34 a	175 ± 34 a
Pour-on treatment	87	131 ± 35 b	51 ± 20 b
Untreated	84	363 ± 41 a	175 ± 56 a
Injectable treatment	53	72 ± 43 b	15 ± 19 b

Means within the same column followed by the same letter are not significantly different ($P = 0.05$).

Table 3. Mean ± SD of IF and percentage control of recovered females of *B. microplus* that at the time treatments were administered were in different parasitic stages on untreated cattle, cattle treated with a single pour-on application of doramectin at 0.5% AI, or cattle treated with a single subcutaneous injection of doramectin at 200 μg AI/kg body weight

Parasitic stage at treatment	IF	Percent control of IF
Pour-on treatment		
Adult	173.2 ± 22.19	89.0 ± 1.4
Nymph	180.9 ± 84.04	85.0 ± 7.0
Larva	109.9 ± 81.27	92.3 ± 5.7
Untreated		
Adult	1,579.4 ± 615.7	—
Nymph	1,208.8 ± 601.9	—
Larva	1,428.0 ± 639.5	—
Injectable treated		
Adult	2.34 ± 4.43	99.7 ± 0.52
Nymph	1.09 ± 2.12	99.8 ± 0.41
Larva	0.98 ± 1.96	99.8 ± 0.43
Untreated		
Adult	213.25 ± 37.07	—
Nymph	130.80 ± 63.34	—
Larva	113.70 ± 76.05	—

There was not a statistically significant effect of parasitic stage on the day of treatment on the IF of groups of ticks that were either adults, nymphs, or larvae when the pour-on was applied ($P = 0.71$), nor was there a significant treatment times parasitic stage interaction ($P = 0.67$). The mean percentage control of the IF values for each parasitic stage were not statistically different ($F = 1.92$; df = 2, 11; $P < 0.20$; Table 3).

The persistent efficacy of the pour-on treatment 1 wk after treatment was 0%. Differences between the mean IF values for ticks collected from the treated and untreated calves for the larval infestation placed on hosts 7 d after treatment were not statistically significant ($F = 0.242$; df = 1, 7; $P = 0.64$).

Doramectin Injectable Treatment. The mean number of engorged females collected per calf in the group that received an injection of doramectin was 84.4% fewer, a statistically significant difference ($F = 9.29$; df = 1, 7; $P < 0.02$) from the mean number of engorged females collected from the untreated calves. The degree of therapeutic control of the IF from the injectable treatment was 99.8% (Table 1). The difference between the mean weights of an engorged female from the treated and untreated groups was statistically significant ($F = 277.0$; df = 7, 136; $P < 0.0001$), as was the difference between the mean egg mass weights ($F = 63.0$; df = 7, 136; $P < 0.0001$; Table 2).

There was a statistically significant effect ($F = 17.1$; df = 5, 23; $P < 0.0001$) of the subcutaneous injection on the IF, but there was not a significant effect ($P > 0.07$) of treatment on the IF of groups of ticks at a different parasitic stage when the calves were injected, and there was not a significant interaction between the treatments and parasitic stage ($P > 0.08$; Table 3).

Estimates of persistent efficacy from comparisons of the mean IF values from data based on the four larval infestations made weekly beginning 1 wk after treatment (Table 4) indicated that differences in percent-

Table 4. Mean percentage control ± SD of the IF of *B. microplus* females that survived to repletion from larval infestations applied to untreated and treated cattle at weekly intervals following a single subcutaneous injection of doramectin at 200 μg AI/kg body weight

Posttreatment larval infestations (week)	Percent control of the IF
1	100 a
2	98.9 ± 2.5 a
3	82.1 ± 10.1 a
4	44.1 ± 28.2 b

Means within the same column followed by the same letter are not significantly different ($P = 0.05$).

age control between the weekly infestations were statistically significant ($F = 10.9$; df = 3,15; $P < 0.001$). Although the percentage of control values for the first three weekly posttreatment infestations ranged from 100 to 82.1, the differences were not statistically different ($P > 0.05$), but the percentage control value for the fourth infestation was significantly lower than the other three ($P < 0.05$).

Discussion

The 88.6% therapeutic control that resulted from a single treatment with the pour-on formulation of doramectin compared favorably with the levels of control reported by Davey and George (2002) for pour-on treatments with eprinomectin (87.7%), ivermectin (84.7), and moxidectin (78.7%). The subcutaneous injection produced an appreciably higher level of control than the pour-on, with a therapeutic efficacy of 99.8%. Gonzales et al. (1993) calculated efficacy of a subcutaneous injection treatment as a comparison between the mean number of engorged female *B. microplus* that detached daily from treated and untreated calves instead of also taking fecundity and fertility into account in the calculation, but they reported a comparable level of therapeutic efficacy of >99%. The female weight and egg mass weight of ticks recovered from the two treatments indicate the difference in the intensity of the effect of the subcutaneous injection versus the pour-on application. The weight of females from the injection treatment was 55% less than for the females from the pour-on treatment. The mean weight of an egg mass from the injection treatment was 71% less than the weight of the egg masses from calves treated with the pour-on formulation.

Without data on the comparative pharmacokinetics of treatments with the two doramectin formulations in relation to efficacy, there is no basis for concluding that a higher concentration of doramectin in the serum of calves who were recipients of the injection treatment was responsible for the greater efficacy of this treatment, but it is likely. The timing for administering treatments in both trials was on the 18th day after the first tick infestation was placed on the hosts. The treatment occurred 2 d before any females completed the engorgement process and detached and provided time for absorption of the active ingredient into the blood and lymph of the calves and ingestion of the drug during the final engorgement process of the first engorged female ticks to detach. Both treatments had similar effects on the ticks that were in the different parasitic life stages at the time of treatment, because with both the pour-on and injection treatments, there was not a statistically significant difference in the IF or percentage control values between ticks that were adults, nymphs, or larvae on the day of treatment.

The persistent efficacies of the two treatment methods are remarkably different. The degree of control of the IF of engorged females that developed from larvae placed on calves 1 wk after treatment with pour-on doramectin was zero. Persistent efficacy from the subcutaneous injection ranged from 100 to 82.1% (mean, 93.7%) for the engorged females that developed from three weekly posttreatment larval infestations and was still at 44% for the fourth posttreatment infestation. In view of the high level of acaricidal activity of doramectin indicated by the >99% therapeutic efficacy and the appreciable persistent efficacy of the injection treatment, it is apparent that concentrations of the drug that were lethal to ticks remain in the hosts' blood a relatively long time. While the initial amount of doramectin absorbed into the bloodstream and available on the skin and hair of the animals treated with the pour-on exposed engorging ticks to quantities of the drug at the threshold of the dose needed to control the majority of the ticks on the host at the time of treatment, the amount of drug had dropped below that level before the 1-wk posttreatment larval infestation occurred.

Both the pour-on and the injectable formulations of doramectin could be used to control *B. microplus* on cattle, but the advantages of the injectable product in terms of both therapeutic and persistent efficacy are obvious. The potential value of the injectable doramectin to the CFTEP with its specialized requirements is also apparent. The injectable formulation could be used for systematic treatment of cattle to eradicate outbreaks of *Boophilus* ticks with treatments scheduled every 21–28 d. If the possible presence of coumaphos-resistant ticks mitigated against the continued use of coumaphos in dipping vats or as a spray, the injectable doramectin could also be used as a precautionary treatment for cattle within the Quarantine Zone to permit them to be moved if they were inspected and no ticks were found. Because of the widespread distribution of populations of *B. microplus* in Mexico that are resistant to coumaphos, the most pressing need of the CFTEP is for an efficacious acaricide to replace coumaphos as a precautionary treatment to ensure that cattle on which inspectors at VS Livestock Import Stations have found no ticks are actually not infested with larval or nymphal *Boophilus* when they are exported to the United States. Because of their large size, engorging female ticks are comparatively easy to find when cattle are inspected by experienced technicians, but the much smaller immature ticks are more difficult to find and more likely to be overlooked when large numbers of cattle are being

processed through an import station. Davey and George (2002) demonstrated that a double application regimen with a 4-d interval between pour-on treatments with ivermectin or eprinomectin would provide 99% or greater control of *B. microplus* on cattle, and it is likely that similar efficacy could be obtained with a double treatment of doramectin pour-on. The double-treatment approach with one of the pour-on products would provide the desired preventative protection against OP-resistant ticks, but the cost and logistical complications of having to hold and feed cattle for 4 d between treatments are major obstacles. In contrast, using an injection of doramectin for the preventative treatment should be relatively simple and straightforward, and unless nearly replete female ticks are overlooked by inspectors, it seems that the treatment would be fully effective against all parasitic stages of *Boophilus* ticks.

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